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Chattopadhyay, Subhayan

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Risk of second primary cancer following myeloid neoplasia and risk of myeloid neoplasia as second primary cancer: a nationwide, observational follow up study in Sweden

Subhayan Chattopadhyay, Guoqiao Zheng*, Amit Sud*, Hongyao Yu, Kristina Sundquist, Jan Sundquist, Asta Försti, Akseli Hemminki, Richard Houlston, Kari Hemminki*

Summary

Background Although advances in the treatment of myeloid neoplasms have led to improved patient survival, this improvement has been accompanied by an increased risk of second primary cancer (ie, the risk of another cancer after myeloid neoplasia). We aimed to assess bi-directional associations between myeloid cancers and other cancers—ie, development of second primary cancer in patients who have previously had myeloid cancer, and risks of myeloid neoplasia in patients who have previously had another cancer—to provide insight into possible mechanisms beyond side-effects of treatment and shared risk factors.

Methods Using the Swedish Family-Cancer Database, we identified 35 928 individuals with primary myeloid cancer, including myeloproliferative neoplasms, acute myeloid leukaemia, chronic myeloid leukaemia, and myelodysplastic syndrome diagnosed between 1958 and 2015. The Swedish Family-Cancer Database includes every individual registered as a resident in Sweden starting in 1932, with full parental history. The primary endpoint was the assessment of relative risks (RRs) for second primary cancer, which we performed using means of incidence rate ratios, regressed over a generalised Poisson model.

Findings Between 1958 and 2015, overall relative risk of second primary cancers was significantly increased after acute myeloid leukaemia (RR 1·29, 95% CI 1·17–1·41), chronic myeloid leukaemia (1·52, 1·35–1·69), myelodysplastic syndrome (1·42, 1·26–1·59), and all myeloproliferative neoplasms (1·37, 1·30–1·43) relative to the incidence of these cancers as first primary cancer. With myeloid neoplasia as a second primary cancer, risks were significantly increased for acute myeloid leukaemia (1·57, 1·48–1·65), chronic myeloid leukaemia (1·26, 1·13–1·40), and myelodysplastic syndrome (1·54, 1·42–1·67) relative to the incidence of these myeloid neoplasms as first primary cancers. Relative risk of upper aerodigestive tract cancer, squamous cell skin cancer, and non-Hodgkin lymphoma as second primary cancers were increased after all four types of myeloid neoplasia relative to their incidence as first primary cancers. High risks of myelodysplastic syndrome and acute myeloid leukaemia as second primary cancers were found after haematological cancers (RRs between 5·08 and 10·04).

Interpretation The relative risks of second primary cancer are important for the long-term management of patients with myeloid cancers. The bi-directional associations of myeloid cancers with many other cancers suggest a number of candidate mechanisms that might contribute to the development and aetiology of a second primary cancer. These mechanisms might include immune dysfunction or the effects of treatment, and these should be assessed in future investigations.

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Introduction

All myeloid cancers originate from the same haemopoietic lineage and are characterised by excessive proliferation, abnormal self-renewal, and differentiation defects.[1,2] The distinct clinical phenotypes are *BCR-ABL1*-negative myeloproliferative neoplasms, polycythaemia vera, essential thrombocythemia, myelofibrosis, chronic myeloid leukaemia, myelodysplastic syndrome, and acute myeloid leukaemia. Polycythaemia vera is characterised by a high erythrocyte count, essential thrombocythaemia by a high platelet count, and myelofibrosis by bone marrow failure. Myelodysplastic syndrome is characterised by ineffective haemopoiesis, morphological dysplasia in haemopoietic cells, and cytopenia.[3] Although myeloproliferative neoplasm subtypes are independent diseases, transformation from myeloproliferative disorders and myelodysplastic syndrome to acute myeloid leukaemia can occur.[2,4]

The causes of myeloid diseases are poorly understood and few risk factors have been identified. Known risk factors for acute myeloid leukaemia include exposure to ionising radiation, chemicals such as benzene, and

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*Joint first authors

Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany (S Chattopadhyay MS, G Zheng MD, H Yu MD, A Försti PhD, Prof K Hemminki MD); **Faculty of Medicine, University of Heidelberg, Heidelberg, Germany** (S Chattopadhyay, G Zheng, H Yu); **Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK** (A Sud MD, Prof R Houlston MD); **Center for Primary Health Care Research, Lund University, Malmö, Sweden** (Prof K Sundquist MD, Prof J Sundquist MD, A Försti, Prof K Hemminki); **Department of Family Medicine and Community Health, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, USA** (Prof K Sundquist, Prof J Sundquist); **Center for Community-based Healthcare Research and Education (CoHRE), Department of Functional Pathology, School of Medicine, Shimane University, Japan** (Prof K Sundquist MD, Prof J Sundquist); **Cancer Gene Therapy Group, Faculty of Medicine, University of Helsinki, Finland** (Prof A Hemminki MD); **Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland** (Prof A Hemminki); **and Division of Molecular Pathology, The Institute of Cancer Research, London, UK** (Prof R Houlston)

Correspondence to:
Subhayan Chattopadhyay
Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany
S.Chattopadhyay@dkfz.de

Research in context

Evidence before this study

We searched PubMed with the search terms "second primary cancer after myeloid disease" and "myeloid disease diagnosed after cancer"; we also applied specific myeloid diseases as search terms. Furthermore, we reviewed the literature cited in the identified papers.

Added value of this study

The present study applied two novel approaches. Using data from 35 928 individuals with myeloid neoplasia registered with the Swedish Cancer Registry, we analysed risk of second primary cancer after all main types of primary myeloid cancer, including myelodysplastic syndrome, which had not previously been assessed in the context of relative risk for second primary cancer. Furthermore, we used bi-directional analysis to assess risk of second primary cancers after myeloid neoplasms, and risk of myeloid neoplasms after any of 32 cancers. Our findings showed that risks of myeloid neoplasms were associated with all haematological cancers. We showed that the increased risk of second primary cancers is not confined to a specific myeloid cancer, and that it is also increased after myelodysplastic syndrome. Bi-directional increases in risk were observed for nine myeloid neoplasia-cancer pairs. Upper aerodigestive tract cancer, squamous cell skin cancer, and non-Hodgkin lymphoma were the major second primary cancers following diagnosis of acute myeloid leukaemia, chronic myeloid leukaemia, myelodysplastic syndrome, and myeloproliferative neoplasm. The results suggest that new mechanisms, such as immune dysfunction, might contribute to bi-directional risks.

Implications of all available evidence

Increased risks of myeloid cancers after melanoma, squamous cell skin cancer, and kidney cancers, all of which are treated mainly by surgery, raise the possibility that immune dysfunction could be a contributing factor to second primary cancers in people who have had myeloid cancer, but this hypothesis requires further studies. Treatment for myeloid neoplasms has undergone many recent changes and therapeutic successes need to be weighed against side-effects, such as risk of second primary cancer.

cytotoxic chemotherapy.[2] For myelodysplastic syndrome risk factors include autoimmune disorders and immunological aberrations.[5–7] Several rare high penetrance mutations in cancer susceptibility genes—such as Janus kinase 2 (*JAK2*), calreticulin (*CALR*), and myeloproliferative leukaemia virus oncogene (*MPL*)—have been identified and are now incorporated in disease classification, for example for myeloproliferative neoplasms.[3,8] Treatment for myeloproliferative disorders aims to reduce the risk of progression and has relied on compounds such as hydroxyurea, inhibiting DNA synthesis, and cytokine interferon alpha, which modulates immune and other functions; more recently specific *JAK-2* inhibitors have been included in treatment.[9] Patients with acute myeloid leukaemia might receive induction treatment with DNA synthesis inhibitors, such as cytarabine and anthracycline, supplemented with hydroxyurea. Consolidation treatment could include cytarabine administration or bone marrow transplantation. Until tyrosine kinase inhibitors were introduced into the standard of care for *BCR-ABL1*-positive patients in about the year 2000, treatment for chronic myeloid leukaemia was hydroxycarbamide, interferon alpha, and allogeneic haemopoietic stem-cell transplantation, and still remains the standard treatment.[10] Treatment options for myelodysplastic syndrome, which depend on diagnostic findings and symptoms, can include multiple modalities. Treatment for first cancers might be an important risk factor for second primary cancers.

Recent advances in the management of all forms of myeloid cancers, including personalised approaches, have greatly improved patient survival. However, this increase in survival has been accompanied by an increase in the number of second primary cancers and other treatment-related complications, such as cardiovascular and neurological symptoms.[11] Several studies have estimated the risks of second primary cancers after myeloid cancer, but most have confined their analyses to acute myeloid leukaemia and chronic myeloid leukaemia, with scant available data for myeloproliferative neoplasms.[9,12–15] This gap in the literature seems to be largely because most cancer registries do not collect data on other myeloid cancers. To address this deficiency, we used data from the Swedish Cancer Registry to analyse all myeloid cancers and second primary cancers after myeloid cancers in Sweden, and myeloid cancers diagnosed as second primary cancers following the occurrence of any non-myeloid first cancer.

Methods

Study design and participants

The Swedish Family-Cancer Database includes data from the Swedish population, organised by families, and linked to the national Cancer Registry. The registry relies on compulsory notifications from clinicians who diagnose any neoplasm and separate notifications from pathologists and cytologists. It includes every individual registered as a resident in Sweden since 1932 with full parental histories. The database's coverage is estimated at more than 90% of all cancer diagnoses in Sweden, with more than 2 million cancers registered since 1958.[16] The registry counts tumours not patients, except in cases where a patient has more than one tumour of the skin or urinary tract diagnosed in the same topological area. To classify cancer types, the Swedish Cancer Registry has used International Classification of Disease (ICD)-7 since 1958, ICD-9 since 1987, SNOMED (ICD-O/2) since 1993, and ICD-O/3 since 2005. The degree of histological verification of myeloid cancers varies from 98% to

100% for acute myeloid leukaemia and chronic myeloid leukaemia, to about 95% for polycythaemia vera and myelofibrosis.[17] An ad hoc study of the diagnostic accuracy of second neoplasms in the Swedish Cancer Registry found 98% of these to be correctly classified; no recorded second primary cancer was found to be a metastasis upon re-examination.[18]

The Swedish Cancer Registry organises reported cancers as first, second, third primary cancer, and so on, and we followed this order. We included data from all patients whose first primary cancer was acute myeloid leukaemia, chronic myeloid leukaemia, myelodysplastic syndrome, polycythaemia vera, essential thrombocythaemia, myelofibrosis, or myeloproliferative neoplasm (not otherwise specified) diagnosed between 1958 and 2015, and were analysed for the relative risk of second primary cancer. In assessing the relative risk of myeloid cancers as a second primary cancer, we included patients with any first primary cancer except leukaemia, to avoid dependency. We selected any of 32 cancers by the main categories of ICD-7. We used ICD-7 and ICD-O/2 codes to distinguish between different haematological cancers and subtypes. Myeloproliferative neoplasms were classified according to the 2016 WHO classification. Myeloproliferative neoplasm (not otherwise specified), myelofibrosis, and myelodysplastic syndrome were distinguished in ICD-O/2, and included as distinct entities in the database from 1993. We excluded rare myeloproliferative neoplasms, such as chronic eosinophilic leukaemia and chronic neutrophilic leukaemia, from our subtype analysis. We did not include data from patients who developed myeloid disease after previous myeloid disease because of the potential for transformation between tumour types. The ICD codes used by the Swedish Cancer Registry do not specify treatment-related cancers, although the literature suggests that treatment-related cancers now account for 7% of acute myeloid leukaemia.[19] The study periods were constrained by the availability of data.

Outcomes and statistical analysis

Relative risks (RRs) for second primary cancers were assessed by means of incidence rate ratios, assuming that cancer diagnoses followed waiting time distribution, regressed over a fixed effects generalised Poisson model. Regression was assessed on case numbers scaled on person-years. This reduced case numbers as compared with the reference fractions in each person-year category. Person-year calculation for the background population ensured large case numbers in each covariate band and met the large number assumption for the Poisson distribution. RRs for the second primary cancer were obtained by comparing incidence of that cancer type in the general Swedish population without previous diagnosis of cancer with the incidence of that cancer type as a second primary cancer in patients who had had myeloid cancer as a first primary cancer. Conversely, to consider myeloid cancers as second primary cancers, the incidence rates were compared against the incidence of the first primary myeloid neoplasm in the background population without a previous cancer diagnosis. These two types of analyses constituted the bi-directional or reciprocal analyses. Sex, age group, calendar-period, socioeconomic status, and residential area were regarded as potential confounders and were adjusted for in the regression model. Confidence intervals (CIs) were calculated for 5%, 1% and 0·1% level of significance.

All analyses were done with SAS (version 9.4) or R (version 3.3.4). The study was approved by the Ethical Committee of Lund University, Sweden, and conducted in accordance with the Declaration of Helsinki.

	First primary cancer	Any second primary cancer*	Median follow up (years)
Sex			
Men	18 816 (52·4%)	1405 (53·4%)	..
Women	17 112 (47·6%)	1226 (46·6%)	..
Year			
1958–70	8334	132 (5·0%)	..
1971–85	7775	542 (20·6%)	..
1986–2000	8551	923 (35·1%)	..
2001–15	11 268	1034 (39·3%)	..
First primary cancer			
Acute myeloid leukaemia	12 832	427 (3·3%)	3 (2–5)
Chronic myeloid leukaemia	5567	306 (5·5%)	3 (2–6)
Myelodysplastic syndrome	3520	259 (7·4%)	1 (0–5)
Polycythemia vera	6636	916 (13·8%)	6 (3–9)
Essential thrombocythaemia	4081	422 (10·3%)	4 (3–10)
Myelofibrosis	1454	118 (8·1%)	2 (0–5)
Chronic neutrophilic leukaemia or chronic eosinophilic leukaemia	204	10 (4·9%)	2 (0–3)
Myeloproliferative neoplasm (not otherwise specified)	1634	173 (10·6%)	3 (1–6)

Data are n (%) or median (IQR). *Second primary cancers after primary myeloid cancers.

Table 1: **Patients with myeloid cancer as first primary cancer (n=15 329 616)**

	Second primary cancer	Median follow-up time in years
Acute myeloid leukaemia	1463 (37·7%)	5 (2–11)
Chronic myeloid leukaemia	380 (9·8%)	6 (3–13)
Myelodysplastic syndrome	750 (19·4%)	6 (3–11)
Polycythaemia vera	474 (12·2%)	8 (3–15)
Essential thrombocythaemia	392 (10·1%)	10 (3–18)
Myelofibrosis	171 (4·4%)	6 (2–14)
Chronic neutrophilic leukaemia or chronic eosinophilic leukaemia	22 (0·6%)	10 (5–14)
Myeloproliferative neoplasm (not otherwise specified)	221 (5·7%)	5 (2–13)

Data are n (%) or median (IQR). Follow-up time is the duration of follow up between diagnosis of first primary cancer and diagnosis of second primary cancer.

Table 2: **Patients with myeloid cancer as a second primary cancer**

For more on **Survey of Nordic Cancer Registries** see https://www.ancr.nu/dyn/resources/File/file/7/4247/1412940269/total_document_survey_optimeret.pdf

For more on the **2016 WHO myeloproliferative neoplasm classification** see https://doi.org/10.1038/s41408-018-0054-y

	Relative risk of second primary cancer after myeloid neoplasia				Relative risk of myeloid neoplasia as second primary cancer			
	N	RR	CI Lower	CI Upper	N	RR	CI Lower	CI Upper
Upper aerodigestive tract	77	1·95*	1·56	2·43	94	1·15	0·94	1·40
Oesophagus	26	1·38	0·95	2·00	6	0·75	0·34	1·66
Stomach	75	0·93	0·74	1·17	66	1·00	0·79	1·27
Small intestine	15	1·71†	1·03	2·84	17	1·66†	1·03	2·67
Colorectum	248	0·97	0·86	1·10	362	1·06	0·95	1·17
Anus	9	2·31‡	1·24	4·30	8	1·37	0·69	2·75
Liver	76	1·21	0·96	1·52	8	0·47†	0·24	0·94
Pancreas	64	1·04	0·82	1·33	7	0·45†	0·21	0·94
Nose	8	3·10*	1·61	5·97	5	0·94	0·39	2·26
Lung	223	1·40*	1·23	1·60	73	1·11	0·88	1·39
Breast	184	0·98	0·84	1·13	624	1·13‡	1·05	1·23
Cervix	12	0·81	0·45	1·47	71	0·91	0·72	1·15
Endometrium	45	1·05	0·78	1·40	179	1·11	0·96	1·28
Ovary	36	1·12	0·80	1·55	110	1·53*	1·27	1·85
Other female genital	6	0·81	0·39	1·70	17	1·22	0·76	1·96
Prostate	419	1·05	0·96	1·16	695	1·30*	1·20	1·40
Testis	3	1·23	0·40	3·80	32	1·91*	1·35	2·70
Other male genital	2	0·58	0·14	2·31	6	0·78	0·35	1·73
Kidney	107	2·07*	1·71	2·51	112	1·54*	1·28	1·85
Bladder	126	1·31‡	1·10	1·56	237	1·40*	1·23	1·59
Melanoma	104	1·84*	1·52	2·23	169	1·27‡	1·09	1·47
Skin SCC	301	2·80*	2·50	3·14	195	1·47*	1·28	1·70
Eye	4	0·72	0·23	2·25	15	1·33	0·80	2·21
Nervous system	90	2·23*	1·82	2·73	88	1·12	0·91	1·38
Thyroid gland	14	1·42	0·86	2·36	73	2·06*	1·64	2·59
Endocrine gland	51	2·24*	1·71	2·94	100	1·25†	1·03	1·52
Bone	4	2·14	0·80	5·70	9	1·50	0·78	2·88
Connective tissue	21	1·99‡	1·30	3·05	29	1·47†	1·02	2·11
Non-Hodgkin lymphoma	119	1·95*	1·62	2·34	239	3·31*	2·91	3·76
Hodgkin's lymphoma	15	2·63*	1·59	4·37	59	4·47*	3·46	5·77
Multiple myeloma	49	1·60*	1·21	2·12	122	4·78*	3·78	6·04
Cancer of unknown primary	89	1·23	1·00	1·51	26	0·98	0·67	1·45
All	2631	1·36*	1·30	1·42	3873	1·32*	1·28	1·37

N=frequency. RR=relative risk. SCC=squamous cell carcinoma. *Statistical significance at 0·1%. †Statistical significance at 5%. ‡Statistical significance at 1%.

Table 3: **Relative risk of second primary cancer in patients with myeloid cancer, and relative risk of second primary myeloid neoplasia in patients who have had other cancers**

See Online for appendix

Role of the funding source

The funders had no role in the design or conduct of the study. KH had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 35 928 patients recorded by the Swedish Cancer Registry with primary myeloid cancer between 1958 and 2015, 1405 men and 1226 women developed a second primary cancer with a median follow up of 4 years (table 1). Acute myeloid leukaemia was the most common primary myeloid cancer (12 832 patients), but only 427 (3%) were diagnosed with a second primary cancer. Of 6636 patients with polycythemia vera, 916 (14%) were diagnosed with a second primary cancer (table 1). Of the 940 811 other patients, 3873 (<1%) developed a myeloid cancer as a second primary cancer (table 2), with a median follow up of 6 years.

We did stratified risk analyses on second primary cancer incidence after myeloid neoplasia, stratifying by time, sex, age at first cancer diagnosis, and duration of follow up between diagnosis of first primary cancer and diagnosis of second primary cancer (appendix pp 2–5). No cases with myelodysplastic syndrome or myeloproliferative neoplasm (not otherwise specified) were recorded in the early study periods, as the coding system for identification of these cases started to be used in 1993 (appendix p 2). RRs for the second primary cancer did not differ between study periods (ie, 95% CIs were overlapping), with the exception of a high RR of 1·81 for myeloproliferative neoplasm between 1971 and 1985, partly caused by the high RR for essential thrombocythaemia. Sex did not affect risk for second primary cancer (appendix p 3) but diagnosis with myeloid neoplasia below the age of 65 years was a strong risk modifier (increased risk), except in patients with myelodysplastic syndrome (appendix p 4). Follow-up time between diagnosis of first primary cancer and diagnosis of second primary cancer did not systematically affect risk of developing a second primary cancer; we noted significantly increased risks of a second primary cancer after myeloid neoplasia in most follow-up periods (appendix p 5). For all patients with myelodysplastic syndrome, maximal follow up was relatively short at 30 years (ie, 1986–2015). We analysed relative risks of a second primary cancer after chronic myeloid leukaemia in more detail, because standard treatment for chronic myeloid leukaemia changed with the introduction of tyrosine kinase inhibitors around the year 2000 (appendix p 6). Although few second primary cancers were recorded in this analysis, we noted significant increases in the risk of upper aerodigestive tract, thyroid, and connective tissue cancers as second primary cancers in the period between 2001 and 2015 relative to the background risk of these cancers as first primaries between 2001 and 2005.

Table 3 shows the RRs of a second primary cancer after a myeloid cancer, and of myeloid cancer as a second primary cancer. Overall, the relative risk of second primary cancer after all myeloid cancers was increased 1·36 (95% CI 1·30–1·42) times relative to the background risk of any first primary cancer diagnosis. An increased risk was shown for 15 cancer sites, notably for nasal cancer (RR 3·10, 95% CI 1·61–5·97), squamous cell skin cancer (2·80, 2·50–3·14), and Hodgkin lymphoma (2·63, 1·59–4·37). These RRs were significant at the 0·1% level. Myeloid cancer as a second primary cancer showed an RR of 1·32 (95% CI 1·28–1·37). Individually,

	Acute myeloid leukemia		Chronic myeloid leukemia		Myelodysplastic syndromes		Myeloproliferative neoplasms	
	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)
Upper aerodigestive tract	16	2·19* (1·34–3·58)	10	2·10† (1·13–3·91)	9	2·29† (1·19–4·41)	42	1·43† (1·06–1·94)
Oesophagus	2	0·55 (0·14–2·22)	4	1·83 (0·69–4·87)	5	2·64† (1·10–6·35)	15	1·16 (1·06–1·93)
Stomach	10	0·73 (0·39–1·36)	14	1·35 (0·80–2·27)	5	1·04 (0·43–2·49)	46	0·92 (0·69–1·23)
Small intestine	2	1·25 (0·31–4·98)	2	2·07 (0·52–8·26)	2	2·12 (0·53–8·48)	9	1·50 (0·78–2·88)
Colorectum	40	0·91 (0·67–1·24)	32	1·24 (0·88–1·75)	23	0·83 (0·55–1·24)	153	0·88 (0·75–1·03)
Anus	3	3·92† (1·26–12·16)	0	..	1	2·02 (0·28–14·35)	5	1·71 (0·71–4·11)
Liver	20	1·82* (1·18–2·83)	6	0·87 (0·39–1·93)	5	1·09 (0·46–2·63)	45	1·14 (0·85–1·53)
Pancreas	12	1·09 (0·62–1·92)	4	0·56 (0·21–1·50)	2	0·43 (0·11–1·72)	46	1·21 (0·90–1·61)
Nose	0	..	1	2·75 (0·39–19·56)	2	8·14* (2·03–32·62)	5	2·51† (1·05–6·05)
Lung	36	1·26 (0·91–1·75)	18	1·06 (0·67–1·68)	30	1·99‡ (1·39–2·85)	139	1·38‡ (1·17–1·63)
Breast	31	0·88 (0·62–1·26)	13	0·60 (0·35–1·04)	9	0·61 (0·32–1·17)	131	0·98 (0·83–1·17)
Cervix	2	0·72 (0·18–2·89)	2	0·90 (0·23–3·61)	0	..	8	0·92 (0·46–1·85)
Endometrium	6	0·73 (0·33–1·64)	13	2·55 (1·48–4·40)	0	..	26	0·85 (0·58–1·25)
Ovary	10	1·60 (0·86–2·98)	2	0·45 (0·11–1·82)	2	1·11 (0·28–4·44)	22	1·04 (0·68–1·57)
Other female genital	0	..	0	..	1	1·30 (0·18–9·25)	5	0·81 (0·34–1·94)
Prostate	72	0·92 (0·73–1·15)	50	1·20 (0·91–1·58)	35	0·60† (0·43–0·84)	262	1·07 (0·95–1·21)
Testis	0	..	1	1·73 (0·24–12·25)	1	8·94† (1·26–63·57)	1	0·83 (0·12–5·89)
Kidney	9	0·98 (0·51–1·88)	16	2·61† (1·60–4·25)	9	2·14† (1·11–4·11)	73	2·12‡ (1·69–2·67)
Bladder	21	1·27 (0·83–1·95)	12	1·28 (0·73–2·25)	17	1·42 (0·88–2·29)	76	1·08 (0·86–1·35)
Melanoma	17	1·55 (0·96–2·49)	6	0·92 (0·42–2·06)	11	1·43 (0·79–2·59)	70	1·75‡ (1·38–2·21)
Skin SCC	37	2·18‡ (1·58–3·01)	47	5·54† (4·16–7·37)	47	2·34‡ (1·76–3·12)	170	1·94‡ (1·67–2·26)
Nervous system	22	2·69‡ (1·77–4·09)	9	1·63 (0·85–3·13)	4	1·29 (0·48–3·43)	55	2·11‡ (1·62–2·76)
Thyroid gland	3	1·56 (0·50–4·83)	3	2·23 (0·72–6·91)	0	..	8	1·13 (0·57–2·26)
Endocrine gland	7	1·57 (0·75–3·30)	2	0·71 (0·18–2·85)	1	0·46 (0·07–3·29)	41	2·55‡ (1·88–3·46)
Bone	1	2·68 (0·38–19·06)	0	..	0	..	3	2·59 (0·83–8·03)
Connective tissue	4	2·06 (0·77–5·48)	4	3·23† (1·21–8·60)	2	1·93 (0·48–7·70)	11	1·55 (0·86–2·80)
Non–Hodgkin lymphoma	18	1·67† (1·05–2·64)	14	2·27* (1·35–3·84)	22	3·17 ‡ (2·09–4·82)	65	1·60‡ (1·25–2·04)
Hodgkin lymphoma	4	3·60† (1·35–9·60)	1	1·20 (0·17–8·53)	0	..	10	2·77‡ (1·49–5·15)
Multiple myeloma	11	2·03† (1·13–3·67)	1	0·31 (0·04–2·17)	6	2·03 (0·91–4·51)	31	1·58† (1·11–2·25)
Cancer of unknown primary	7	0·54 (0·26–1·14)	15	2·00† (1·20–3·31)	7	0·97 (0·46–2·04)	60	1·31† (1·02–1·69)
All	427	1·29‡ (1·17–1·41)	306	1·52‡ (1·35–1·69)	259	1·42‡ (1·26–1·59)	1639	1·37‡ (1·30–1·43)

N=frequency; RR=relative risk. SCC=squamous cell carcinoma. *Statistical significance at 1%. †Statistical significance at 5%. ‡Statistical significance at 0·1%.

Table 4: **Relative risk of second primary cancer among survivors of myeloid cancer**

15 cancers were associated with an increased risk of myeloid cancer, most notably cancers of the haematopoietic system: non-Hodgkin lymphoma (RR 3·31, 95% CI 2·91–3·76), Hodgkin's lymphoma (4·47, 3·46–5·77), and myeloma (4·78, 3·78–6·04). We recorded bi-directional increases for nine myeloid neoplasia-cancer pairs, including cancers of the small intestine, kidney, bladder, skin (both melanoma and squamous cell carcinoma), connective tissue, and haemapoietic tissue (table 3).

Table 4 shows the RRs of all non-myeloid second primary cancers after a first diagnosis of acute myeloid leukaemia, chronic myeloid leukaemia, myelodysplastic syndrome, or myeloproliferative neoplasm. The overall RRs for second primary cancers after each of these four diseases were 1·29 (95% CI 1·17–1·41), 1·52 (1·35–1·69), 1·42 (1·26–1·59), and 1·37 (1·30–1·43), respectively. The numbers of individual non-myeloid second primary cancers with increased RRs were 8 for acute myeloid leukaemia, 7 for chronic myeloid leukaemia, 8 for myelodysplastic syndrome, and 12 for myeloproliferative neoplasm. Risk of upper aerodigestive tract cancer, skin squamous cell carcinoma, and non-Hodgkin lymphoma was increased irrespective of myeloid primary type. Risk of kidney cancer was increased in patients with a first primary cancer diagnosis of chronic myeloid leukaemia, myelodysplastic syndrome, and myeloproliferative neoplasm relative to the background risk. For acute myeloid leukaemia, high RRs were noted for anal cancer (RR 3·92, 95% CI 1·26–12·16) and Hodgkin's lymphoma (3·60, 1·35–9·60). The RR for skin squamous cell carcinoma was 5·54 (95% CI 4·16–7·37) after chronic

myeloid leukaemia. Myelodysplastic syndrome was associated with a high risk of non-Hodgkin lymphoma (RR 3·17, 95% CI 2·09–4·82). After a first primary cancer diagnosis of myeloproliferative neoplasm, the highest RRs were noted for Hodgkin's lymphoma (RR 2·77, 95% CI 1·49–5·15), followed by endocrine (2·55, 1·88–3·46), nasal (2·51, 1·05–6·05), kidney (2·12, 1·69–2·67), and nervous system (2·11, 1·62–2·73) cancers relative to the background risk of developing that cancer as a first primary cancer risk.

When comparing RRs between cancer-pairs between tables 4 and 5, we noted bi-directionally increased RRs for acute myeloid leukaemia with six cancers, for chronic myeloid leukaemia two cancers, for myelodysplastic syndrome with four cancers, and for myeloproliferative neoplasm with four cancers. The RRs for both reciprocal associations of acute myeloid leukaemia and haematological cancers and anal cancer were high.

We assessed RRs for second primary cancers after different subtypes of myeloproliferative neoplasm. The overall RRs for diagnosis of any second primary cancer after polycythaemia vera, essential thrombocythaemia, myelofibrosis, or myeloproliferative neoplasm (not otherwise specified) were 1·34 (95% CI 1·25–1·43), 1·39 (1·27–1·54), 1·88 (1·64–2·17), and 1·50 (1·28–1·76), respectively, compared with risk of any first primary cancer (table 6). Polycythaemia vera as a first primary cancer was associated with increased risk for 11 second primary cancers; essential thrombocythemia and

	Acute myeloid leukemia		Chronic myeloid leukemia		Myelodysplastic syndrome		Myeloproliferative neoplasms	
	N	RR (95%CI)	N	RR (95%CI)	N	RR (95%CI)	N	RR (95%CI)
Upper aerodigestive tract	39	1·42* (1·03–1·94)	11	1·14 (0·63–2·07)	16	1·48 (0·91–2·42)	28	0·81 (0·56–1·17)
Oesophagus	2	0·71 (0·18–2·85)	2	2·26 (0·57–9·05)	2	1·69 (0·42–6·75)	0	..
Stomach	21	0·85 (0·56–1·31)	10	1·18 (0·64–2·20)	11	1·45(0·8–2·62)	24	0·97 (0·65–1·45)
Small intestine	5	1·51 (0·63–3·63)	2	1·90 (0·47–7·59)	4	2·37 (0·89–6·32)	6	1·38 (0·62–3·07)
Colorectum	135	1·21* (1·02–1·44)	40	1·15 (0·84–1·58)	73	1·25 (0·99–1·58)	115	0·80 (0·67–0·96)
Anus	7	3·88† (1·85–8·13)	0	..	0	..	1	0·39 0·05–2·77)
Liver	4	0·65 (0·24–1·73)	3	1·61 (0·52–4·99)	1	0·41 (0·06–2·93)	0	..
Pancreas	1	0·17 (0·02–1·18)	1	0·53 (0·07–3·74)	2	1·04 (0·26–4·17)	3	0·53 (0·17–1·64)
Nose	3	1·66 (0·53–5·14)	0	..	0	..	2	0·92 (0·23–3·66)
Lung	26	1·16 (0·79–1·70)	9	1·28 (0·66–2·46)	18	1·79* (1·13–2·85)	20	0·74 (0·48–1·15)
Breast	249	1·43† (1·26–1·62)	74	1·29* (1·03–1·63)	83	0·94 (0·76–1·17)	219	0·92 (0·80–1·05)
Cervix	42	1·61‡ (1·19–2·18)	5	0·49 (0·20–1·18)	9	0·96 (0·50–1·85)	15	0·46* (0·28–0·76)
Endometrium	72	1·41‡ (1·11–1·77)	25	1·53* (1·03–2·27)	32	1·16 (0·82–1·64)	50	0·72* (0·54–0·95)
Ovary	61	2·55† (1·98–3·28)	8	0·97 (0·49–1·95)	16	1·58 (0·97–2·59)	25	0·83 (0·56–1·23)
Other female genital	9	1·92* (1·00–3·69)	1	0·64 (0·09–4·52)	3	1·49 (0·48–4·61)	4	0·69 (0·26–1·85)
Prostate	219	1·31† (1·15–1·50)	73	1·57† (1·24–1·98)	159	1·45† (1·23–1·70)	244	1·06 (0·93–1·20)
Testis	14	2·58† (1·53–4·37)	6	2·60* (1·17–5·79)	5	2·50* (1·04–6·02)	7	0·98 (0·47–2·06)
Kidney	33	1·35 (0·96–1·90)	14	1·76* (1·04–2·97)	14	1·28 (0·76–2·17)	51	1·68† (1·28–2·21)
Bladder	85	1·57† (1·27–1·95)	23	1·38 (0·91–2·08)	44	1·49‡ (1·11–2·01)	85	1·16 (0·94–1·44)
Melanoma	38	0·95 (0·69–1·30)	16	1·24 (0·76–2·02)	29	1·20 (0·83–1·73)	86	1·45† (1·17–1·79)
Skin SCC	45	1·09 (0·81–1·46)	19	1·51 (0·96–2·38)	49	1·92† (1·45–2·55)	82	1·45† (1·17–1·81)
Nervous system	36	1·39* (1·00–1·92)	4	0·45 (0·17–1·20)	12	1·03 (0·58–1·81)	36	1·09 (0·79–1·52)
Thyroid gland	20	1·72* (1·11–2·67)	5	1·23 (0·51–2·97)	9	1·80 (0·94–3·47)	39	2·61† (1·91–3·58)
Endocrine gland	25	0·99 (0·67–1·47)	10	1·26 (0·68–2·35)	13	0·94 (0·54–1·62)	52	1·48‡ (1·13–1·95)
Bone	5	2·44* (1·02–5·87)	1	1·32 (0·19–9·34)	1	1·26 (0·18–8·98)	2	0·82 (0·20–3·26)
Connective tissue	10	1·55 (0·83–2·88)	1	0·45 (0·06–3·21)	5	1·68 (0·70–4·03)	13	1·55 (0·90–2·66)
Non–Hodgkin lymphoma	119	5·16† (4·31–6·19)	10	1·42 (0·76–2·46)	76	6·03† (4·80–7·57)	34	1·10 (0·79–1·55)
Hodgkin's lymphoma	35	7·69† (5·52–10·72)	1	0·55 (0·08–3·89)	15	10·04† (6·05–16·68)	8	1·50 (0·75–2·99)
Myeloma	76	8·71† (6·95–10·91)	1	0·36 (0·05–2·58)	35	9·45† (6·77–13·19)	10	0·96 (0·51–1·78)
Cancer of unknown primary	11	1·16 (0·64–2·10)	3	1·00 (0·32–3·09)	5	1·37 (0·57–3·28)	7	0·68 (0·32–1·43)
All	1463	1·57† (1·48–1·65)	380	1·26† (1·13–1·40)	750	1·54† (1·42–1·67)	1280	1·02 (0·96–1·08)

N=frequency. RR=relative risk. SCC=squamous cell carcinoma. *Statistical significance at 5%. †Statistical significance at 0·1%. ‡Statistical significance at 1%.

Table 5: **Relative risk of myeloid cancer after first primary cancer**

myelofibrosis were both associated with increased risk of seven secondary primary cancers; and myeloproliferative neoplasm (not otherwise specified) was associated with increased risk of developing second primary cancer at nine cancer sites relative to the background rates for these cancers. All myeloproliferative neoplasms were associated with an increased risk of developing skin squamous cell carcinoma as a second primary cancer, with the greatest risk after myelofibrosis (RR 3·71, 95% CI 2·27–6·05). Relative risks of nervous system cancer were increased after polycythaemia vera, essential thrombocythaemia, and myelofibrosis; risks of non-Hodgkin lymphoma were increased after polycythaemia vera, myelofibrosis, and myeloproliferative neoplasm (not otherwise specified). Risk of other female genital cancers (RR 3·31, 95% CI 1·38–7·96) was increased only in patients who had had essential thrombocythaemia. Risk of Hodgkin's lymphoma (RR 12·26, 95% CI 3·95–18·03) was increased in patients with previous myelofibrosis.

We assessed the risk of myelioproliferative neoplasms as second primary cancers after other cancers (appendix p 7). With the exception of kidney and thyroid cancers, no other cancers were observed to have increased risk throughout most of the subtypes of myeloproliferative neoplasms. We noted we noted reciprocal associations confirming increased bi-directional risk for six unique cancer-myeloproliferative neoplasm pairs (melanoma, kidney, and connective tissue cancer paired with

	Polycythemia vera		Essential thrombocythemia		Myelofibrosis		Myeloproliferative neoplasm (not otherwise specified)	
	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)
Upper aerodigestive tract	20	1·44 (0·93–2·23)	10	1·66 (0·89–3·09)	5	2·82* (1·17–6·77)	7	3·27† (1·56–6·85)
Oesophagus	10	1·41 (0·76–2·62)	5	1·61 (0·67–3·88)	0	..	0	..
Stomach	32	1·01 (0·71–1·43)	12	1·26 (0·71–2·21)	1	0·30 (0·04–2·11)	1	0·32 (0·04–2·26)
Small intestine	3	1·02 (0·33–3·15)	4	2·93* (1·10–7·81)	0	..	2	4·09* (1·02–16·38)
Colorectum	77	0·89 (0·71–1·12)	38	0·94 (0·68–1·29)	13	1·19 (0·69–2·05)	24	1·66* (1·11–2·48)
Anus	4	2·93* (1·10–7·81)	1	1·34 (0·19–9·53)	0	..	0	..
Liver	30	1·29 (0·90–1·84)	6	0·70 (0·31–1·56)	5	1·78 (0·74–4·27)	4	1·39 (0·52–3·70)
Pancreas	23	1·02 (0·68–1·54)	13	1·40 (0·79–2·46)	4	1·45 (0·54–3·86)	6	2·04 (0·91–4·53)
Nose	3	2·94 (0·95–9·12)	1	2·42 (0·34–17·23)	0	..	1	6·99 (0·98–49·70)
Lung	86	1·57‡ (1·27–1·94)	32	1·31 (0·93–1·86)	6	0·85 (0·38–1·89)	15	1·73* (1·04–2·87)
Breast	76	1·23 (0·98–1·54)	39	1·18 (0·86–1·61)	6	0·85 (0·38–1·90)	9	0·83 (0·43–1·60)
Cervix	3	0·66 (0·21–2·03)	3	1·59 (0·51–4·94)	0	..	2	3·54 (0·88–14·14)
Endometrium	15	1·04 (0·63–1·73)	9	1·18 (0·62–2·27)	1	0·59 (0·08–4·19)	1	0·40 (0·06–2·81)
Ovary	12	1·03 (0·58–1·81)	5	1·05 (0·44–2·51)	1	0·76 (0·11–5·43)	3	2·03 (0·65–6·29)
Other female genitals	0	..	5	3·31 (1·38–7·96)	0	..	0	..
Prostate	156	1·25† (1·07–1·47)	63	1·15 (0·90–1·48)	21	1·11 (0·72–1·70)	20	0·87 (0·65–1·35)
Testis	1	1·97 (0·28–13·99)	0	..	0	..	0	..
Kidney	46	2·51‡ (1·87–3·36)	18	2·44‡ (1·52–3·93)	5	2·22 (0·92–5·33)	4	1·65 (0·62–4·38)
Bladder	49	1·53† (1·15–2·02)	19	1·24 (0·79–1·94)	2	0·49 (0·12–1·94)	6	1·07 (0·48–2·38)
Melanoma	37	2·27‡ (1·65–3·14)	23	2·26‡ (1·50–3·40)	4	1·66 (0·62–4·42)	6	1·60 (0·72–3·56)
Skin SCC	73	2·19‡ (1·74–2·76)	52	2·57‡ (1·95–3·38)	16	3·71‡ (2·27–6·05)	26	3·45‡ (2·35–5·06)
Nervous system	29	2·17‡ (1·51–3·13)	16	2·63‡ (1·61–4·29)	6	3·29† (1·48–7·32)	4	1·88 (0·71–5·01)
Thyroid gland	2	0·58 (0·15–2·34)	3	1·94 (0·63–6·02)	0	..	3	5·59† (1·80–17·33)
Endocrine gland	26	3·49‡ (2·38–5·13)	11	3·10‡ (1·72–5·61)	1	0·94 (0·13–6·70)	3	2·41 (0·78–7·49)
Bone	2	3·27 (0·82–13·08)	0	..	1	12·31* (1·73–87·47)	0	..
Connective tissue	6	1·70 (0·76–3·79)	2	1·25 (0·31–5·01)	2	4·35* (1·09–17·38)	1	1·75 (0·25–12·40)
non-Hodgkin lymphoma	31	1·59* (1·12–2·26)	14	1·42 (0·84–2·40)	7	2·64* (1·26–5·53)	12	3·29‡ (1·87–5·80)
Hodgkin's lymphoma	3	1·55 (0·50–4·80)	2	2·74 (0·69–10·98)	3	12·26† (3·95–38·03)	2	8·19* (2·05–32·76)
Multiple myeloma	17	1·64* (1·02–2·64)	0	..	0	..	2	1·21 (0·30–4·84)
Cancer of unknown primary	33	1·30 (0·93–1·83)	13	1·16 (0·67–2·00)	6	1·86 (0·84–4·14)	8	1·98* (1·09–3·95)
All	916	1·34‡ (1·25–1·43)	422	1·39‡ (1·27–1·54)	118	1·88‡ (1·64–2·17)	173	1·50‡ (1·28–1·76)

N=frequency. RR=relative risk. SCC=squamous cell carcinoma. *Statistical significance at 5%. †Statistical significance at 1%. ‡Statistical significance at 0·1%.

Table 6: **Relative risk of second primary cancers among patients with different subtypes of myeloproliferative neoplas**

polycythemia vera; squamous cell carcinoma of skin paired with myelofibrosis; and small intestine cancer and non-Hodgkin lymphoma paired with myeloproliferative neoplasm (not otherwise specified).

Discussion

To address a paucity of data regarding the development of second primary cancers after myeloproliferative neoplasms, we used data from the Swedish Cancer Registry to analyse all myeloid cancers and second primary cancers in Sweden, and myeloid cancers diagnosed as second primary cancers after any non-leukaemic first cancer, between 1958 and 2015. Our analysis provides further evidence that survivorship from a myeloid cancer is associated with a statistically significant relative risk of a second primary cancer. We showed that the increased relative risk is not confined to any one myeloid cancer, and is also increased after myelodysplastic syndrome. The relative risk of upper aerodigestive tract cancer, skin squamous cell carcinoma, and non-Hodgkin lymphoma were the major second primary cancers after previous acute myeloid leukaemia, chronic myeloid leukaemia, myelodysplastic syndrome, and myeloproliferative neoplasm. Our results thus provide new systematically analysed information on the risk of diverse types of second primary cancers, and validate and expand previous observations.[9,10,12–15]

A major strength of our study, as compared with other analyses, is the avoidance of ascertainment bias in patient selection by using a registry that includes data from the entire Swedish population, with high proportions of case registration and long-term follow up. To the best of our knowledge, this is the first study to apply systematic bi-directional analysis for second primary cancer after myeloid cancer and myeloid cancer as second primary cancer. We used data from the largest population of myeloid neoplasms yet published.[9]

The limitations include unavailability of some myeloid neoplasms before year 1993 and no information on treatment, in addition to the inherent weaknesses of observational studies in deducing disease causation. Although the coverage of the Swedish Cancer Registry is high, it might not be equally high for some newly established diagnostic categories, such as myelodysplastic syndrome. Other factors that are difficult to control for are reporting practices of second primary cancers.

Treatment-related side-effects are generally considered to be the cause of many second primary cancers following treatment for a myeloid cancer.[20] However, such a mechanism is unlikely to be the sole cause for all second primary cancers; there might be several mechanisms underlying the increased risk of a second primary cancer risk in patients who have had myeloid cancer. Although treatment for the myeloid cancers is heterogeneous and has changed over time, many patients—and certainly those in our cohort diagnosed before the year 2000—are likely to have received one or more types of cytoreductive treatment during their disease course.[4,21] Hydroxyurea has been used as first line cytoreductive treatment for myeloproliferative neoplasm in many patients. An increased risk of non-melanoma skin cancer during hydroxyurea treatment has been reported, and people have hypothesised that hydroxyurea could act as a photosensitiser and thus, in combination with ultraviolet radiation exposure, increase the risk of skin squamous cell carcinoma.[22] However, this mechanism is not likely to be the cause of a myeloproliferative cancer that develops after a first primary skin squamous cell carcinoma because this type of skin cancer is usually treated by surgery. By contrast, side-effects of other chemotherapeutic agents such as anthracyclines might have contributed to the increased risk of second primary cancers after myeloid neoplasia, such as in cases of lung and upper aerodigestive tract cancers. We showed a possible increase in relative risk in cases with upper aerodigestive tract cancer after chronic myeloid leukaemia diagnosed between 2001 and 2015 as compared with the earlier study periods, which a previous small Swedish study suggested might have been associated with the use of tyrosine kinase inhibitors.[10] We noted that testicular cancer was associated with an increased risk of acute myeloid leukaemia, chronic myeloid leukaemia, and myelodysplastic syndrome. Testicular cancer is treated with radiotherapy and a combination of drugs that damage DNA, such as bleomycin, etoposide, and cisplatin, which might be an explanation for the increased risk of second myeloid neoplasia.[23]

In this study, myeloid neoplasms were associated with all haematological cancers that might have had acquired immune dysfunction due to cytotoxic treatment or bone marrow transplantation as an underlying mechanism.[24] Inherited mechanisms might also contribute to the development of myeloid neoplasms through master regulators of haemopoiesis, including transcriptional regulators of critical steps in cell development such as STAT5, CEBPα, PU.1, and CITED2, among others.[25] Their expression is controlled at the genetic or epigenetic level, and aberrations in their expression might have pleiotropic effects on several cell lineages. For example, loss of the genetic regulator *GATA-2* has been shown to suppress haemopoiesis and contribute to immunodeficiency.[26] Changes in the expression of other epigenetic regulators, such as *IDH*, *TET2*, and *BCAT1* genes, might have similar effects.[27] Given that many cancer susceptibility genes have pleiotropic effects it is plausible that the risk of a second primary cancer is influenced by inherited genetic factors, either through high penetrance alleles or co-inheritance of multiple common risk variants. Patients with myeloid neoplasia have an increased risk of non-haematological cancers prior to their diagnosis of myeloproliferative neoplasm, and first-degree relatives of patients with myeloproliferative cancer have an increased risk of myeloproliferative neoplasms and chronic lymphocytic leukaemia—as well

as melanoma and brain cancer—which is consistent with germline susceptibility to myeloproliferative and other cancers.[28,29] Although risks of other cancers in families of patients with myeloid neoplasia are yet to be established, common genetic variants of *TERT* associated with risk of myeloproliferative neoplasia have also been shown to influence glioma and other cancers.[30] Familial risks might also be a contributing factor. We have previously published the results of a study of discordant associations between all common cancers using data from the Swedish Family-Cancer Database, and shown that discordant familial risks do exist but RRs are small, in the order of 1·1–1·2 for most cancer pairs.[31]

On the other hand, because myeloid diseases and their treatment can be associated with immunosuppression, this raises the possibility that impaired tumour immunosurveillance could play a part in the development of second primary cancers in patients with previous myeloid cancer.[24] The contribution of immune dysfunction in these cancers might be compounded by germline susceptibility. For example, germline mutations in *GATA2* have been reported to contribute to immune deficiency in haematological cancers, including familial myelodysplastic syndrome and acute myeloid leukaemia.[32] We have provided evidence of bi-directional associations between myeloid cancers and lymphomas, and between lymphomas and skin squamous cell carcinoma, kidney cancer, and bladder cancer. Increased risk of second primary cancer in patients with myeloid cancer is probably multifactorial. A combination of cytoreductive treatment, genetic predisposition, and immune-related effects might all contribute to an increased cancer risk in survivors of myeloid cancers.

In conclusion, we have provided a comprehensive analysis of cancer risks associated with myeloid cancers using observational data from a comprehensive cancer registry. We propose putative mechanisms that might contribute to these associations, such as immune disturbances acting together with cytotoxic and genetic effects. Future studies are clearly warranted to investigate such potential mechanisms in detail—for example, by assessing immune competence as a predictor of second primary cancer, and the effects of immunotherapy on the risk of second primary cancers. Our findings substantiate the well-known risks of developing second primary cancers after surviving each of the myeloid cancers, and help inform the long-term management of patients successfully treated for these tumours, who should be monitored for the occurrence of second primary cancers.

Contributors

KH, AS, and SC designed the study. KH was in charge of the overall project supervision and management. JS and KS acquired data. SC, GZ, AS, HY, and KH did statistical analysis and interpretation. KH, RH, AS, AH, and AF wrote the manuscript. All authors approved the final text.

Declaration of interests

AH is shareholder in Targovax ASA. AH is employee and shareholder in TILT Biotherapeutics Ltd. All other authors declare no competing interests.

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